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12/05/97 JC408 U.S. PTO

To: Assistant Commissioner for Patents
Box Patent Applications
Washington D.C. 20231

Attorney Docket No.040388/0110
(must include alphanumeric codes if no inventors named)

UTILITY PATENT APPLICATION TRANSMITTAL
(new nonprovisional applications under 37 CFR 1.53(b))

Transmitted herewith for filing is the patent application of:

INVENTOR(S): Jean-Francois BACH and Lucienne CHATENOUD

TITLE:METHOD FOR TREATING ESTABLISHED SPONTANEOUS AUTO-IMMUNE DISEASES IN MAMMALS

In connection with this application, the following are enclosed:

APPLICATION ELEMENTS:

XX Specification - 13 TOTAL PAGES

(preferred arrangement:)

-Descriptive Title of the Invention
-Cross Reference to Related Applications
-Statement Regard Fed sponsored R&D
-Reference to Microfiche Appendix
-Background of the Invention
-Brief Summary of the Invention
-Brief Description of the Drawings (if filed)
-Detailed Description
-Claim(s)
-Abstract of the Disclosure

XX Drawings - Total Sheets 1

__ Declaration and Power of Attorney - Total Sheets __

_ Newly executed (original or copy)

_ Copy from a prior application (37 CFR 1.63(d))

(relates to continuation/divisional boxes completed) - NOTE: Box below

__ DELETION OF INVENTOR(S) - Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).

__ Incorporation By Reference (useable if copy of prior application Declaration being submitted)

The entire disclosure of the prior application, from which a COPY of the oath or declaration is supplied as noted above, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

__ Microfiche Computer Program (Appendix)

__ Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)

__ Computer Readable Copy
__ Paper Copy (identical to computer copy)
__ Statement verifying identify of above copies

The PTO [illegible] the following listed [illegible] Assignment

ACCOMPANYING APPLICATION PARTS

__ Assignment Papers (cover sheet & document(s))
__ 37 CFR 3.73(b) Statement (when there is an assignee)
__ English Translation Document (if applicable)
XX Information Disclosure Statement(IDS) with PTO-1449. 1 Copies of IDS Citations

XX Preliminary Amendment
XX Return Receipt Postcard (MPEP 503)
____ Small Entity Statement(s)
__ Statement file in prior application, status still proper and desired.
____ Certified Copy of Priority Document(s) with Claim of Priority (if foreign priority is claimed).
____ OTHER:

If a **CONTINUING APPLICATION**, **check appropriate box and supply the requisite information:**
__ Continuation __ Divisional __ Continuation-in-part (CIP) of prior application Serial No. __.

__ Amend the specification by inserting before the first line the following sentence: --This application is a __ continuation, __ divisional or __ continuation-in-part of application Serial No. __, filed __.--

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FEE CALCULATIONS: (Small entity fees indicated in parentheses.)

(1) For	(2) Number Filed	(3) Number Extra	(4) Rate	(5) Basic Fee $790 ($395)
Total Claims	15 - 20 =	0	x $22 (x $11)	0.00
Independent Claims	1 - 3 =	0	x $82 (x $41)	0.00
Multiple Dependent Claims			$270 ($135)	0.00
Assignment Recording Fee per property			$40	
Surcharge Under 37 C.F.R. 1.16(e)			$130 ($65)	130.00
			TOTAL FEE:	$920.00

METHOD OF PAYMENT:
A check in the amount of the above TOTAL FEE is attached. If payment by check is NOT enclosed, it is requested that the Patent and Trademark Office advise the undersigned of the period of time within which to file the TOTAL FEE. If payment enclosed, this amount is believed to be correct; however, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 19-0741.

Respectfully submitted,

for Stephen A. Bent (28,665)
Reg. No. 29,768

Date: December 5, 1997
Docket No.: 040388/0110

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 040388/0110

In re patent application of
Jean-Francois BACH et al.
Serial No.: Unassigned
Filed: December 5, 1997
For: METHOD FOR TREATING ESTABLISHED SPONTANEOUS AUTO-IMMUNE DISEASES IN MAMMALS

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination of the above-identified application, Applicants respectfully request that the following amendments be entered into the application:

IN THE CLAIMS:

Please amend the claims as follows:

Claim 7, line 1, delete "or 5".

Claim 8, line 1, delete "or 5".

Claim 11, after "claim 1", insert --,--.

Claim 12, after "claim 1", insert --,--.

Claim 13, after "claim 1", insert --,--.

Attorney Docket No.: 040388/0110

REMARKS

Entry of the foregoing amendments prior to examination is respectfully requested.

Amendments to Claims 7 and 8 are requested by Applicants in order to avoid this application incurring a surcharge for the presence of one or more multiple dependent claims.

Respectfully Submitted,

December 5, 1997

for Stephen A. Bent (28,665)
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Method for treating established spontaneous auto-immune diseases in mammals.

The invention relates to a method for treating established and ongoing spontaneous auto-immune diseases in mammals.

In order to suppress T cell function, immunotherapy based on the use of antibodies directed at T cell surface receptors, particularly of monoclonal antibodies (mAbs), has been extensively investigated. Particularly, mAbs directed against the CD3 complex of the T cell receptor have been shown to cause transient T-cell depletion and antigenic modulation of the CD3-T cell receptor complex.

In PNAS USA, vol. 91, p 123-127, 1994 Immunology, the inventors, with other co-authors, have reported that a short term treatment with low doses of an anti-CD3 mAb could restore self tolerance to ß-cell-associated antigens, thus inducing complete and durable remission of the spontaneous auto-immune diabetes, in overtly diabetic NOD (non obese diabetic) mice.

By further investigating the mode of action of anti-CD3 mAb in this model, the inventors have found that the long term effect was obtained only when treating animal at a very advanced disease stage, i.e. overt auto-immunity. They also demonstrate that non mitogenic, $F(ab')_2$ fragments of the entire CD3 mAb, that are much

better tolerated than the whole entire CD3-mAb, also afford a long term *in vivo* effect in overtly diabetic NOD mice as did the whole anti-CD3 mAb.

This finding is an unexpected extension of the published data which until now, in both transplantation and antigen and/or pharmacologically induced auto-immunity, has proposed $(Fab')_2$ fragments of anti-CD3 mAb as effective tools to only achieve immunosuppression (an overall depression of immune responses that is only maintained through the chronic administration of the drugs), but not to promote permanent antigen-specific unresponsiveness namely, a state of immune tolerance (an antigen-specific immune unresponsiveness that is maintained in the absence of chronic generalized immunosuppression).

Such results are useful for application to other auto-immune situations where similar immunoregulatory mechanisms, such as those present in auto-immune diabetes, have been observed.

Accordingly, an object of the invention is to provide a method of treatment of spontaneous and ongoing of auto-immune diseases in mammals to achieve permanent Ag-specific unresponsiveness, without the morbidity and with a minimal humoral response as that encountered when administering the whole mitogenic antibody.

Another object of the invention is to provide effective tools useful for such a method of treatment.

According to the invention, the method of treating auto-immune diseases in mammals comprises

administering to a mammal, in need of such a treatment, a therapeutically effective amount of one or more non mitogenic anti-CD3 active principles to achieve permanent disease remission through the induction of antigen-specific unresponsiveness, i.e. immune tolerance.

Such a treatment was shown to be able to promote durable remission of the established disease without the clinical side effects involved when administering mitogenic whole anti-CD3 antibodies.

Particularly preferred non mitogenic anti-CD3 antibodies are monoclonal antibodies or fragments thereof, especially $F(ab')_2$ fragments.

Said fragments are advantageously such as obtained by pepsin digestion of the whole antibody.

In view of their therapeutical use, said active principle(s) are highly purified and particularly endotoxin-free.

Said non mitogenic anti-CD3 monoclonal antibody, or fragment thereof is of murine origin or is an humanized antibody.

The permanent antigen-specific unresponsiveness obtained with said anti-CD3 active principles make them particularly useful as therapeutic tools for treating auto-immune pathologies. In particular, they are suitable for treating diabetes, rheumatoïd arthritis, multiple sclerosis or psoriasis.

In said applications, they will be administered, if desired, in combination with other active ingredients and/or compounds which facilitate their assimilation.

Said therapeutical tools are advantageously administered in combination with pharmaceutical carriers under the form of pharmaceutical preparations.

Different forms of administration may be used, especially for injectable route.

The injectable forms contain 5 to 20 mg of active principle per unit dose, preferably from 5 to 10 mg.

For information only, the dose which can be used in the treatment of auto-immune diseases in humans, for example diabetes, is 5 to 10 mg/day for 10 to 14 consecutive doses.

Other characteristics and advantages of the invention will appear from the examples given hereinbelow.

Example 1 : Treatment of overtly diabetic NOD female mice with purified $F(ab')_2$ fragments of CD3 anti-mAb.

NOD mice (K^d, $I\text{-}A^{NOD}$, D^b) were bred under specific pathogen-free conditions ; in females, spontaneous IDDM appears by 14 weeks of age (90 % incidence at 30 weeks of age) and is preceded by insulitis at 4 to 6 weeks.

In a preferred embodiment of the invention said non mitogenic anti-CD3 active principle is a non mitogenic anti-CD3 antibody or a fragment thereof. Such fragments are advantageously $F(ab')_2$ fragments.

The cell line producing the hamster 1452C11 mAb (IgG, anti-mouse CD3 ε-chain) was used in those experiments (O.M. Les et al, 1987, PNAS USA 84:1374).

The anti-CD3 mAb $F(ab')_2$ fragments were prepared by pepsin digestion.

Pepsin (Sigma Chemical Co., St. Louis, MO) was used at a final concentration of 2 % (20 µg/mg of purified antibody) in 1M acetate buffer, pH 3. Digestion was conducted for 2 h at 37°C. Following dialysis at 4°C using 0.1 M PBS pH 8, digested $F(ab')_2$ fragments were purified in two steps : a protein A-Sepharose CL-4B affinity chromatography column to eliminate digested Fc fragments, then gel filtration of the nonretained fraction on an Ultragel AcA54 column (Pharmacia, Uppsala, Sweden).

The physico-chemical properties of the fragment preparations were analyzed by SDS-PAGE.

The binding capacity was tested by immunofluorescence in a classical competition assay using purified FITC-labeled whole CD3 mAb.

The digestion and purification of $F(ab')_2$ fragments was performed with special caution to avoid endotoxin contamination. The material used for *in vivo* treatment was negative in the *Limulus* assay.

NOD females presenting with overt diabetes were included in the treatment protocol when a fasting glycemia ranging 3.5 to 4 g/L was scored on two

consecutive occasions. Mice were then randomized to receive a treatment with CD3 mAb $F(ab')_2$ fragments (50 µg/day for 5 consecutive days), whole CD3 mAb (5-20 µg/day for 5 consecutive days), or as a control normal hamster Igs.

Complete remission was defined as a return to normal glycemia and the disappearance of glycosuria in the absence of any exogenous insulin supply. Histopathology on paraffin sections of Bovin-fixed or frozen pancreatic tissue were performed as previously described (1). Scoring of mononuclear cell infiltration was as follows : grade 0 = normal islets ; grade 1 = focal or peripheral insulitis (lymphocytes around the islet, but no destruction of endocrine cells as assessed by labeling with anti-insulin Abs) ; and grade 2 = invasive destructive insulitis.

The results regarding the remission of overt diabetes in the mice following the short treatment with purified $F(ab')_2$ fragments are given in Table 1.

Table I

Weeks After Treatment	% Remission of IDDM	
	Anti-CD3 $F(ab')_3$ n = 42	Hamster 1g n = 18
0	0	0
2	55	22
4	62	16
6	64	0
10	67	0
20	67	0

The difference in percent remission between CD3 mAB $F(ab')_2$ fragments-treated and control animals is statistically significant ($p<0.01$) using χ^2 test.

As shown by said results, $F(ab')_2$ fragments of the mAb appeared potent in promoting permanent remission of overt diabetes in the conditions of the experiments.

Example 2 : Study of the triggering effect of $F(ab')_2$ fragments of CD3 mAb on cytokine gene transcription.

NOD females received a single i.v. injection of either intact 145 2C11 CD3 mAb (20 μg) or purified $F(ab')_2$ fragments of 145 2C11 CD3 mAb (50 μg). Mice injected with saline or with 5 to 50 μg of L2, a hamster mAb specific for recombinant but not natural mouse IL-2, were used as controls. Three individual animals were analyzed in each group. Spleen cells were collected before any treatment and at various times following injection of the different preparations, and RNA was extracted for RT-PCR.

Crude RNA was extracted using TRIzol (Life Technologies) followed by isopropanol precipitation. For reverse transcription (RT), total RNA (6 μl in a final volume of 12 μl) was added to 18 μl of cDNA synthesis reaction mixture. Two microliters of RT product was amplified using PCR for 30 cycles. final volume of 50 μl, with standard buffer conditions and a final Mg^{2+} concentration of 1.5 mM (2.5 U Taq UNA polymerase, Life Technologies). Each PCR cycle consisted of 1 min at 94°C, 1 min at 55°C, and 1 min at 72°C on a Techne thermal cycler (Osi, Paris, France) ; 100 ng of cDNA was used for PCR unless stated otherwise. When needed to semi-quantitate the amplification products obtained, PCR with doubling dilutions of cDNA was performed. The following primers (Bioprobe Systems, France) were used : IFN-γ 5' primer, CCA GCA GAG AAT GGA AAG TC ; IFN-γ 3' primer. GAT GCT GCT TAC ATG TCT CG ; IL.2 5' primer CCA GCA GAG AAT GGA AAG

TC; IL-2 3' primer, GAT GCT GCT TAC ATG TCT CG ; IL-4 5' primer. TCG GCA TTT TGA ACG AGG TC, IL-4 3' primer. GAA AAG CCC GAA AGA GTC TC ; IL-10 5' primer, GGG ATG ACA GTA GGG GAA CC ; IL-10 3' primer, AGA GCA AGG CAG TGG AGC AG: $ß_2$-microglobulin 5' primer, CCA GCA GAG AAT GGA AAG TC $ß_2$-microglobulin 3' primer, GAT GCT GCT TAC ATG TCT CG. Ten microliters of RT-PCR products were separated by 1.2 % agarose gel electrophoresis in 1 X TBE (Tris-borate-EDTA) containing 0.2 μg/ml of ethidium bromide and visualized under UV light. Where products were semiquantified, RT-PCR, $ß_2$ microglobulin mRNA was used as a housekeeping reporter gene.

The kinetics of mRNA expression is shown in figure 1, part A. Semiquantification of amplification products was performed using doubling dilutions of cDNA for PCR reactions ; data are shown for IL-2, IL-4, and IL-10 in figure 1, part B.

As shown in Figure 1A, using PCR on splenocytes from anti-CD3 $F(ab')_2$-treated animals, enables identification of the transcription of mRNAs specific for IL-2, IL-4, IL-10, and IFN-γ. Semiquantification using serial dilution of cDNA samples suggested that, as compared with what was observed in NOD mice treated with intact CD3 mAb, $F(ab')_2$ fragments promote a less effective transcription of IL-2 mRNA, whereas similar levels of IL-4, II-10, and IFN-γ message were detected (Fig.1B).

Example 3 : Cytokine production by stimulated spleen cells from CD3 mAb- and $F(ab')_2$-treated NOD mice.

Spleen cells from CD3 mAb- and $F(ab')_2$ - treated NOD mice were collected at different times after treatment and tested for their capacity to secrete IFN-γ and IL-4 upon mitogenic stimulation using Con A.

Spleen cells from CD3 or $F(ab')_2$ fragments-treated animals were collected and cultured *in vitro* (1 x 10°/ml) in 24-well plates, for 24 to 48 h in a humidified atmosphere containing 5% CO_2, in DMEM-Glu- tamax (Life Technologies, Paisley, Scotland) supplemented with 100 IU/ml penicillin, 100 μg/ml streptomycin, sodium pyruvate, nonessential aminoacids, 0.05 mM ß-mercaptoethanol, and 10 % FCS. In stimulated cultures, Con A was added at a final concentration of 10 μg/ml. Supernatants were collected and stored frozen at -80°C until tested. IFN-γ and IL-4 were quantitated using specific ELISA as already described (17). The Abs used for detection were AN18 (kindly provided by Dr. A. O'Garra, DNAX, Palo Alto, CA) and biotinylated R46A2 for IFN-γ and 11B11 and biotinylated BVD6 (kindly provided by A. O'Garra) for IL-4, Mouse rIL-4 (R&D Systems. Minneapolis, MN) and IFN-γ were used as internal standards. Detection limits were 0.2 ng/ml for IL-4 and 0.1 ng/ml for IFN-γ.

The results are given in Table 2

Table 2

Treatment	Time from Treatment (week)	IFN-γ (ng/ml)
Anti-CD3	2	68.36 ± 11.51*
Anti-CD3 $F(ab')_2$	2	16.37 ± 3.40*
Hamster Ig	2	101.90 ± 13.34*
Anti-CD3	7	31.74 ± 4.14[5]
Anti-CD3 $F(ab')_2$	7	23.21 ± 5.69[1]
Hamster Ig	7	35.76 ± 4.20
Untreated controls		29.42 ± 7.11

As compared with age-matched controls injected with irrelevant hamster Ig, polyclonally activated spleen cells from CD3 mAb- and $F(ab')_2$ fragment-related NOD mice showed, for about 5 wk from the end of treatment, a significantly decreased IFN-γ- producing ability (Table II).

Example 4 : Pharmaceutical formulation

The active principles are formulated under a desaggregated form and either lyophilyzed or suspended into an appropriate liquid, each dose containing, as above mentioned, 5 to 20 mg of non mitogenic antibody or a fragment thereof.

CLAIMS

1/ A method of treating spontaneous and ongoing autoimmune diseases in mammals, comprising administering to a mammal, in need of such a treatment, a therapeutically effective amount of one or more non mitogenic anti-CD3 active principles to achieve permanent disease remission through the induction of antigen-specific unresponsiveness, i.e. immune tolerance.

2/ The method of claim 1, wherein said non mitogenic anti-CD3 active principle is a non mitogenic anti-CD3.

3/ The method of claim 1, wherein said antibody non mitogenic anti-CD3 active principle is a non mitogenic anti-CD3 $F(ab')_2$ fragment.

4/ The method of claim 1, wherein said non mitogenic anti-CD3 active principle is a non mitogenic anti-CD3 monoclonal antibody.

5/ The method of claim 1, wherein said non mitogenic anti-CD3 active principle is a non mitogenic anti-CD3 monoclonal antibody $F(ab)_2$ fragment.

6/ The method of claim 1, wherein said non mitogenic anti-CD3 active principle is highly purified, endotoxin-free.

7/ The method of claim 4 or 5, wherein said monoclonal antibody is selected from the group consisting of murine or humanized antibody.

8/ The method of claim 3 or 5, wherein said $F(ab')_2$ fragment is such as obtained by pepsin digestion of the whole antibody.

9/ The method of claim 1, wherein said auto-immune disease is diabetes.

10/ The method of claim 1, wherein said auto-immune disease is rheumatoïd arthritis.

11/ The method of claim 1 wherein said auto-immune disease is psoriasis.

12/ The method of claim 1 wherein said auto-immune disease is multiple sclerosis.

13/ The method of claim 1 wherein said active principle is administered by injectable route.

14/ The method of claim 13, wherein said active principle is under the form of injectable solutions, these solutions containing per unit dose from 5 to 20 mg of active principle.

15/ The method of claim 14, wherein said active principle is under the form of injectable solutions, these solutions containing per unit dose from 5 to 10 mg of active principle.

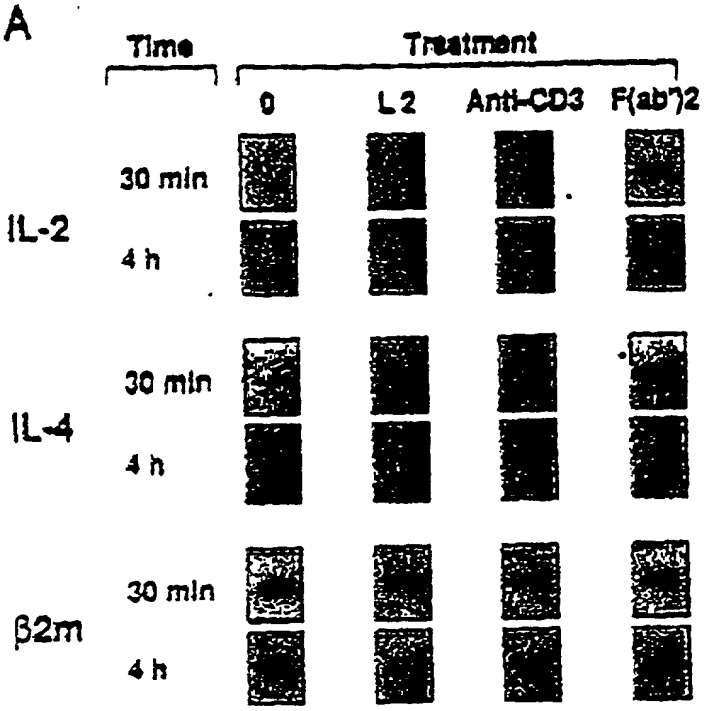
Abstract

A method of treating spontaneous and ongoing auto-immune diseases in mammals, comprising administering to a mammal, in need of such a treatment, a therapeutically effective amount of one or more non mitogenic anti-CD3 active principles to achieve permanent disease remission through the induction of antigen-specific unresponsiveness, i.e. immune tolerance.

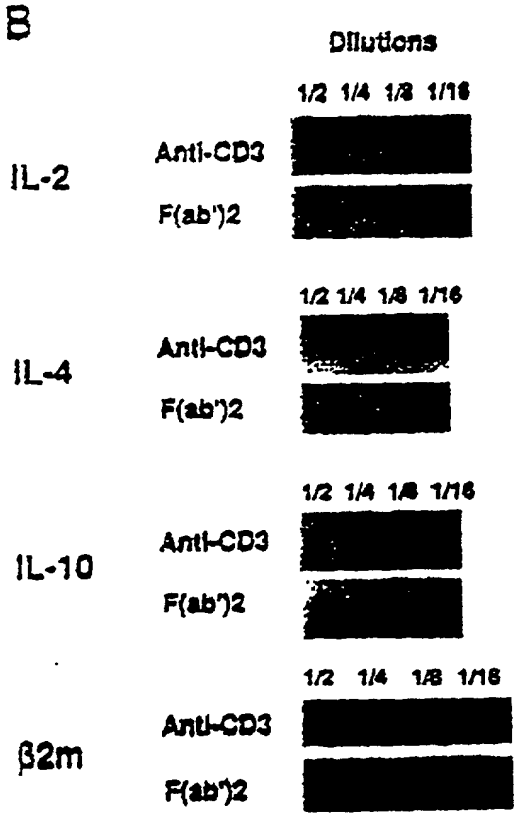
(no figure)

Figure 1

1 A



1 B



Docket No. 040388/0110

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD FOR TREATING ESTABLISHED SPONTANEOUS AUTO-IMMUNE DISEASES IN MAMMALS

the specification of which is attached hereto unless the following box is checked:

☒ was filed on *December 5, 1997* as United States Application Number or PCT International Application Number _____ and was amended on *December 5, 1997* (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is known by me to be material to patentability as defined in Title 37, Code of Federal Regulations § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN APPLICATION(S)

NUMBER	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

APPLICATION NO.	FILING DATE

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is known by me to be material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

APPLICATION SERIAL NO.	FILING DATE	STATUS: PATENTED, PENDING, ABANDONED

I hereby appoint as my attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Stephen A. Bent, Reg. No. 29,768; David A. Blumenthal, Reg. No. 26,257; William T. Ellis, Reg. No. 26,874; John J. Feldhaus, Reg. No. 28,822; Patricia D. Granados, Reg. No. 33,683; John P. Isacson, Reg. No. 33,715; Donald D. Jeffery, Reg. No. 19,980; Eugene M. Lee, Reg. No. 32,039; Richard Linn, Reg. No. 25,144; Peter G. Mack, Reg. No. 26,001; Brian J. McNamara, Reg. No. 32,789; Sybil Meloy, Reg. No. 22,749; George E. Quillin, Reg. No. 32,792; Colin G. Sandercock, Reg. No. 31,298; Bernhard D. Saxe, Reg. No. 28,665; Charles F. Schill, Reg. No. 27,590; Richard L. Schwaab, Reg. No. 25,479; Arthur Schwartz, Reg. No. 22,115; Harold C. Wegner, Reg. No. 25,258.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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